Labeling of HPMA-based, functionalized polymer-systems using metallic radionuclides

Eppard, Elisabeth[1]; Allmeroth, Mareli[2]; Zentel, Rudolf[2]; Roesch, Frank[1]

[1]Institute of Nuclear Chemistry, Johannes Gutenberg-University, Mainz, Germany
[2]Institute of Organic Chemistry, Johannes Gutenberg-University, Mainz, Germany

The aim of this study is the synthesis and evaluation of several different DOTA-spacer-systems for functionalization of HPMA-based polymers. By introducing the bifunctional chelator DOTA, a broad pool of radionuclides becomes available for labeling. These possible variations allow the visualization of the biological behavior over different periods of time depending on the half-life of the used radionuclide (^{68}Ga $T_{1/2}$ = 68 min; ^{44}Sc $T_{1/2}$= 3.9 h). Additionally, the usage of different imaging modalities or endoradiotherapy can be applied depending on the employed radionuclide (^{68}Ga (PET); ^{111}In (SPECT); Gd (MRT); ^{90}Y/^{177}Lu (Therapy)).

The coupling between the chelator and various polymers was facilitated via several spacer units with variable length and structure.

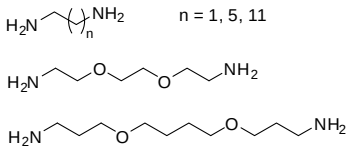

Figure 1: Structure of different spacer systems

The spacers carry two amino-functions, in α- and ω-position, and thus can be coupled to the polymer and the chelator via amid-formation using activated esters. Reductive removal of the ^{t}Bu-groups led to the final labeling precursor.

The DOTA-functionalized polymer-systems were labeled with ^{68}Ga. One conjugate (EEP2L1) was a labeled with ^{44}Sc and ^{177}Lu. The quality control of the complex formation was performed by radio-TLC. The TLC plates were developed with 0.1M citric buffer (pH = 4). Quantitative distribution of radioactivity on TLC plates was measured using an instant imager. Stability studies were performed with NaCl, EDTA, DTPA, Fe^{3+}, Ca^{2+}, Mg^{2+} and human serum with the ^{68}Ga labeled compounds.

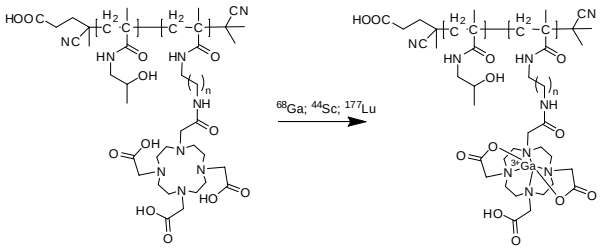

Figure 2: Labeling of the DOTA-functionalized HPMA-polymer

From all studied solutions aliquots were taken after 1, 10, 25, 40, 60, 80 and 120 min and analyzed by TLC.

The spacer synthesis, the coupling to DOTA-tris(^{t}Bu)-ester and the reductive deprotection were successfully accomplished and optimized. We obtained, depending on the used spacer, 50-70% of the corresponding DOTA-spacer-system. These systems were coupled to HPMA-based polymers via amid formation and deprotected with TFA quantitatively. The achieved DOTA-functionalized polymer-system EEP2L1 was effectively labeled with all three radionuclides at 95 °C by 15 – 30 min heating and the labeling for ^{68}Ga was optimized. The ^{68}Ga-labeling procedure was successfully adopted for all conjugates.

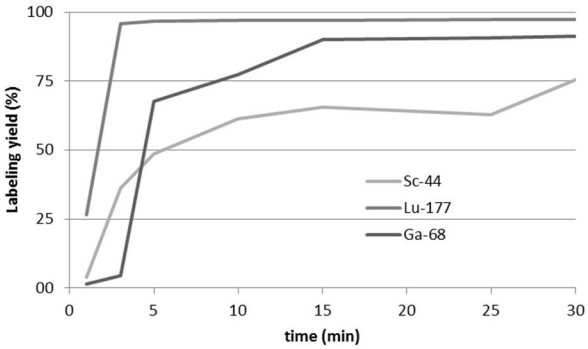

Figure 1: Labeling yields for EEP2L1 in dependence on reaction times with ^{68}Ga, ^{44}Sc and ^{177}Lu

The radiolabeled polymeric systems can be isolated from unreacted radiometal by Sephadex G-25 size exclusion chromatography.
Most of the conjugates show high stability against transmetallation to transferrin and other chelators in *in vitro* studies.

Different chelator-spacer-systems were successfully synthesized and purified, coupled to a polymer and deprotected. Labeling conditions were optimized for EEP2L1 using ^{68}Ga and adopted to other conjugates. Labeling with three different radionuclides (^{68}Ga, ^{44}Sc and ^{177}Lu) was successfully performed for EEP2L1. The functionalized HPMA-polymers will be evaluated pharmacologically in *in vivo* μ-PET studies.

*Acknowledgements:*This work was supported by the Dr. Georg-Scheuing Stiftung.